SHOCK, CEREBRAL HYPOXIA, AND PULMONARY VASCULAR CONTROL: THE CENTRINEUROGENIC ETIOLOGY OF THE RESPIRATORY DISTRESS SYNDROME*

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OUR research was designed to test the hypothesis that the pulmonary changes of the respiratory distress syndrome (RDS), such as follow shock (shock lung), respiratory hypoxia (high-altitude pulmonary edema), birth trauma (hyaline membrane disease [HMD]), or prolonged exposure to hyperbaric oxygen (oxygen toxicity), have a common centrineurogenic etiology. We believe the initiating insult is a disturbance in cerebral oxidative metabolism, probably of the hypothalamus.

Pulmonary venular tone increases as a result of continued autonomic dysfunction. This can lead to the entire complex noted in the pulmonary complication—increased pulmonary vascular resistance, engorgement of small vessels, capillary hypertension, edema, hemorrhage, surfactant inactivation, atelectasis and, occasionally, hyaline membranes.

Pulmonary arterial and venous vessels both possess smooth muscle capable of varying resistance to blood flow. Increased resistance on the arterial side would result in increased pulmonary-artery pressure and work of the right ventricle, and could affect the distribution of blood within the total pulmonary mass. Increasing resistance distal to the capillaries would have these effects and, additionally, could open nonfunctional capillaries (recruitment) for more efficient gas ex-

*Presented as part of a *Symposium on the Multiply Injured Patient* held by the Section on Orthopedic Surgery of the New York Academy of Medicine, January 22, 1973.

This study was supported in part by a grant from the John A. Hartford Foundation, New York, N. Y.; contract DADA 17-73-C-2121 from the U.S. Army Medical Research and Development Command; and a grant from the National Tuberculosis and Respiratory Disease Association, New York, N. Y.

change. Within a wide range, reported as high as 24 mm. Hg,[1] capillary hypertension should not result in alteration of fluid equilibrium. Exceeding this limit or otherwises shifting the equilibrium balance results in transudation of fluid into the pulmonary tissues and alveoli, with deterioration of the lung as an organ of gas exchange.

Both respiratory hypoxia and hemorrhagic shock are known to cause a profound rise in pulmonary vascular resistance.[2, 3] In the case of the latter, it has been shown that during shock there is significant elevation of resistance in the venules and that this becomes even more pronounced after reinfusion of the shed blood.[4] This response is mediated by peripheral nervous communications, and can be abolished in a single lung subjected to immediately prior denervation (autotransplantation), while the normally innervated contralateral lung demonstrates the development of the pathological pattern.[5, 6]

The detrimental effects of shock are accepted to be metabolic derangements secondary to impaired perfusion of tissue. Of all tissues, those of the central nervous system are most sensitive to deprivation of oxygen. The relative sparing of the brain during shock is of short duration, and it soon shares the full impact of reduced cardiac output.[7] Within five minutes the cerebral lactate level doubles.[8] Levels of potassium and pseudocholinesterase in the cerebrospinal fluid rise rapidly; this is evidence of cellular metabolic derangement.[9, 10] In dogs a "standard" hemorrhage regimen, to a mean arterial pressure of 40 mm. Hg, results in a decline of cerebral pO_2 from 65 to 24 mm. Hg.[11]

The pulmonary lesions can be induced in guinea pigs put into a hypobaric chamber to produce an arterial pO_2 of 40 mm. Hg.[12] Despite cerebral malfunction, this level of hypoxemia is not itself lethal to cerebral tissue. Aided by ventilatory support, human patients with arterial pO_2 less than 20 mm. Hg became long-term survivors, without residual neurological deficit.[13]

Paradoxically, elevation of cerebral pO_2 also results in impairment of oxidative metabolism. This was shown to result from "poisoning the catalyst," with oxidation of enzyme sulfhydral bonds, reduction in O_2 consumption, and decrease in cerebral ATP.[14] Indeed, acute oxygen toxicity is manifested by convulsions, as well as by the lung lesions of RDS. For rats subjected to hyperbaric oxygen, both the neutral and pulmonary impairment were prevented by anesthesia.[15] It has become evident that the damage to the lung is not attributable solely to exposure

of the pulmonary tissue to high-inspired pO_2, but parallels elevated arterial pO_2. When the lungs of a dog are intubated differentially, while one lung breathes air and the other breathes 100% O_2, the lesions appear in both.[16] Ventilation of a small fraction of the pulmonary mass with hyperbaric O_2 failed to produce the lesions locally or remotely.[17]

Essential to our research plan is a perfusion technique that provides complete arterial isolation of the brain without disturbing cerebral (or pulmonary) function. The brain possesses a multiplicity of arterial inflow vessels (collaterals), which intercommunicate through low-resistance channels: e.g., the circle of Willis. We developed a benign "positive differential pressure" perfusion technique, which permitted delivery of the total cerebral arterial flow by way of a single cannulated vessel, the common carotid artery. Pressure was monitored downstream within the perfused vessel. When the rate of flow within this vessel was raised sufficiently to exceed aortic pressure by approximately 10 to 20 mm. Hg, it was found that arterial isolation had been accomplished. This rate was approximately 105 to 110% of the basal total flow rate. The terminal cerebral arteries had virtually unchanged perfusion pressures and flow rates. By means of angiograms and isotopic markers it was shown that the excess 5 to 10% of perfusate flowed retrograde from the circle of Willis down the collateral (contralateral carotid and vertebral) arteries, thereby excluding them from contributing to cerebral blood flow.[18, 19] This was found in all species of laboratory animals studied, including subhuman primates.[20] We then utilized this technique to deliver hypoxemic venous blood to the brain while maintaining normal systemic arterial pO_2, pressure, and volume.[21-23]

Perfusion was performed for two hours (pO_2 35 $\pm$ 5 mm. Hg, pCO_2 43 $\pm$ 5 mm. Hg); two hours later the animals were sacrificed. Fifty subjects of seven species—27 dogs, nine calves, five pigs, four monkeys, two sheep. two rabbits, and one goat—developed the gross and microscopic pulmonary changes.[24] The process proved lethal within 20 hours to six dogs not sacrificed. All (18:18) dogs monitored showed deteriorating pulmonary function; arterial pO_2 fell from 86 $\pm$ 7 to 62 $\pm$ 16 mm. Hg despite hyperventilation, reflected by a decline of pCO_2 from 40 $\pm$ 4 to 27 $\pm$ 7 mm. Hg. Newborns (seven calves and three piglets) proved to be very sensitive; none survived even the two hours of perfusion. Four calves died within 20 minutes, and most newborns (8:10) died during the first hour of perfusion, with advanced pulmonary le-

sions indistinguishable from HMD. Left atrial pressure was monitored in six days and showed no evidence of left-ventricular failure.

Another series of 23 dogs was perfused after having been subjected to left pulmonary denervation (autotransplantation) two months previously. These provided the only survivors of our hypoxemic perfusion regimen, although periods up to 48 hours in length were required for complete disappearance of neurological symptoms. Seven animals were sacrificed two hours after perfusion. The left lungs were anatomically intact, while the right lungs showed the acute changes of RDS.

Diphenylhydantoin is a neuropharmacological agent whose mechanism of action remains obscure. However, it is known to permit maintenance of cerebral oxidative metabolism and function during cerebral hypoxia.[25, 26] Standard modification of the Wigger's hemorrhagic shock model led to the development of pulmonary lesions in six dogs of a series of six and in seven rats of a series of eight. When pretreated with diphenylhydantoin, none of a group of eight dogs and only three of 11 rats developed the pulmonary lesions.

For control dogs placed in a chamber with 100% O_2 at ambient pressure, five of six developed the bilateral pulmonary lesions. In five dogs that had had left pulmonary denervation (autotransplantation) two months prior to O_2 exposure, none of the left lungs developed the pulmonary changes. For four of these dogs the contralateral, normally innervated right lungs developed the anatomical changes; one did not.

In summary, our work shows that isolated cerebral hypoxemia, simulating the stagnant hypoxia of shock and the hypoxic hypoxia of rapid ascent, induce the pulmonary complex of RDS. There is no evidence that left ventricular failure is part of this pathological picture. These lesions of shock lung and high altitude pulmonary edema as well as of oxygen toxicity can be averted by pulmonary denervation. Diphenylhydantoin provides pulmonary prophylaxis in hemorrhagic shock. These findings lend support to the hypothesis that these pulmonary syndromes are centrineurogenic and probably are a consequence of disturbed oxidative metabolism in the hypothalamus. Autonomically mediated pulmonary venular spasm would then lead to the entire complex observed.

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